REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Claims 1-38 are currently pending. Claims 1-10 and 28-32 are drawn to the elected invention. Claims 11-27 and 33-38, drawn to non-elected inventions, were withdrawn from consideration by the Examiner and are hereby canceled with this amendment. Claims 1 and 28 currently amended. New claim 39 is added.

Support for the amendment to claim 1 can be found on page 22, lines 5-9 of the specification. Support for new claim 39 can be found on, e.g., in paragraph 88 of the specification. No new matter is added with this amendment.

II. REJECTIONS UNDER 35 USC §112 FIRST PARAGRAPH

Claims 1-10 and 28-32 are rejected under 35 U.S.C. §112, first paragraph because the claims are said to encompass subject matter that has not been described in sufficient detail to enable one of ordinary skill in the art to make or use the invention without undue experimentation. The Examiner specifically alleges that the specification does not reasonably provide enablement for a method of identifying an agent that binds to the CCX-CKR2 of SEQ ID NO:2, by contacting a plurality of agents to a CCX-CKR2 polypeptide comprising 95% identity to SEQ ID NO:2, or a fragment of SEQ ID NO:2 and selecting an agent that competes with I-TAC or SDF1 for binding to the said CCX-CKR2 polypeptide.

As described in greater detail below, the Applicants respectfully disagree for at least the following two reasons: (i) the Office is applying an incorrect enablement standard, and (ii) the rationale presented in the Office Action is inconsistent with statements in the Guidelines promulgated by the Office.

However, before presenting the substantive arguments surrounding the enablement rejection, the Applicants wish to clarify some preliminary matters raised by the Examiner's comments in the Office Action.

First, on page 4 of the Office Action, the Examiner refers to "...a fragment of SDF1 or I-TAC...." It appears the Examiner has misread the claims. The claims recite an "SDF1 or I-TAC binding fragment". The fragment refers to a fragment of the extracellular domain of CCX-CKR2 that binds SDF1 or I-TAC. Agents that bind to this fragment will compete with SDF1 or I-TAC for binding to CCX-CKR2.

Second, the Examiner notes that the specification describes CCX-CKR2 polypeptides as comprising the amino acid sequence set forth in SEQ ID NO:2, 4, 6, 8, or 10 and states that "[i]t is understood that CCX-CKR2 of SEQ ID NO:2 is used in the methods disclosed in this application, unless Applicant contends otherwise." *See*, page 4 of the Office Action. Applicants do not understand the Examiner's statement. Applicants point out that SEQ ID NOs:1, 3, 5, 7, and 9 are nucleic acids encoding CCX-CKR2 polypeptides shown in SEQ ID NOs:2, 4, 6, 8, and 10, respectively. As disclosed in the specification (bottom of page 19 to the top of page 20) any of these nucleic acid and polypeptide sequences can be used for protein expression, or for generation of variants, derivatives, or other sequences derived from a CCX-CKR2 polypeptide suitable for use with the methods as described herein. *See*, page 19, line 30 to page 20, line 10 of the specification.

With the above clarifications in mind, the substantive arguments surrounding the enablement rejection can now be addressed.

The Examiner implies that the specification fails to enable the polypeptides that are recited in the current claims unless the disclosure enables one of ordinary skill to predict which polypeptides would have the recited chemokine binding activity. This is not the appropriate standard for enablement.

When evaluating enablement, the standard was clearly set forth by the court in *In re Wands*:

> The test for enablement is not merely quantitative, since a considerable amount of experimentation is permissible, *if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed*. (*In re Wands*, 8 USPQ2d, 1400, 858 F.2d 731 (Fed. Cir. 1988), emphasis added).

Thus, based on this holding by the Federal Circuit, experimentation is not deemed to be undue if EITHER of two requirements are satisfied: (1) the experimentation is routine, OR (2) the specification provides reasonable guidance in the direction the experimentation should proceed. Although only *one* of these criteria need be satisfied, it is submitted that the specification satisfies *both.*

With respect to the first criterion, the issue is whether one of ordinary skill in the art can routinely (a) make a polypeptide that is a fragment or variant of SEQ ID NO:2, wherein the variant has 95% sequence identity to SEQ ID NO:2 and (b) determine whether such a fragment or variant has the recited chemokine binding activity. It is submitted that the answer to both of these inquiries is "yes."

With respect to issue (a), a copy of a section from the well-known 1992 Devlin Textbook of Biochemistry is enclosed. This section states that:

> By altering or mutating selected regions or single nucleotides within cloned DNA...it is possible to define the role of DNA sequences in gene regulation and amino acid sequences in protein function. Site directed mutagenesis is the controlled alteration of selected regions of a DNA molecule. It may involve the insertion or deletion of selected DNA sequences or the replacement of a specific nucleotide with a different base." ((Devlin, T.M., Ed.) "Textbook of Biochemistry with Clinical Correlations 3rd Edition" Wiley-Liss, Inc. New York, NY, 1992, page 793).

Since this edition of Devlin significantly predates the priority date of the instant application, a skilled artisan could have readily made fragments and variants such as recited in the current claims, as of the priority date of the application. With respect to issue (b), the specification describes a variety of assays that can be utilized to detect binding between the CCX-CKR2 polypeptides and the chemokines SDF-1 and/or I-TAC as recited in the claims. *See,* page 22, line 1 to page 23, line 31 of the specification. Some of the assays described in this section are based on published assays and are thus routine in the art. Furthermore, the Patent Office has taken the view that making variants having 95% identity to a claimed sequence and

retaining activity is conventional in the art. *See*, page 53, Example 14 of the "Synopsis of Application of Written Description Guidelines" promulgated by the Patent Office.

In view of the above, it is clear that a skilled artisan can make polypeptides that share 95% identity with SEQ ID NO:2 using routine techniques, and that the Patent Office considers this conventional in the art. The resulting polypeptides, or fragments thereof, can then be analyzed for their ability to bind the recited chemokines using the routine assays described in the specification. This is all that the law requires to satisfy the requirements of criterion (i) listed above. For this reason alone, it is submitted that the current methods are thus enabled and the Applicants respectfully request that the rejection be withdrawn.

Nonetheless, it is also submitted that the specification satisfies criterion (ii), because the specification provides guidance on the direction that experimentation should proceed. Specifically, the specification provides ample detail and guidance on which amino acid positions could potentially be altered and with what amino acids without unduly affecting activity. The specification, for instance, teaches that variants can involve conservative substitutions. *See*, page 12, lines 9-16 of the specification. The specification goes on to list specific examples of conservative substitutions and cites to a 1984 Creighton reference for further guidance on this issue. *See*, page 12, lines 17-27 of the specification.

Further, the specification provides five exemplary CCX-CKR2 sequences (SEQ ID NOs:2, 4, 6, 8, and 10) with varying amino acid sequences. These sequences provide additional guidance as to areas where amino acid substitutions may be made. For example, SEQ ID NO:4 has an (A) at position 9 and 361, as opposed to an (S) and (T) respectively in the other sequences. Likewise, SEQ ID NO:4 and 10 have an (S) at position 130, as opposed to a (G) in the other sequences. Finally, position 228 is a (V) in SEQ ID NO:6, and an (I) in the other 4 sequences. Furthermore, the specification indicates that CCX-CKR2 is a member of the GPCR family and shares the conserved seven-transmembrane motif. *See e.g.*, page 2, lines 15-19 and page 7, lines 4-5 of the specification. Thus, one of skill in the art would recognize that one logical approach to making variants and generating fragments of SEQ ID NO:2 that would retain binding activity recited in the claims would be to make alterations in non-conserved regions with

other chemokine receptors and GPCRs, as such regions would likely tolerate differences or deletions.

Because the criteria established by the Federal Circuit do not require *predictive* ability to satisfy the enablement requirement, the references cited in the Office Action on this point are irrelevant.

In light of the discussion above showing that a skilled artisan could generate polypeptides having at least 95% sequence identity with SEQ ID NO:2, or SDF1 or I-TAC binding fragments thereof using routine experimentation based on the methods and guidance provided in the specification, the Applicants respectfully request that the Examiner withdraw the rejection.

REJECTIONS UNDER 35 USC §112, SECOND PARAGRAPH

Claims 1-10 and 28-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner has raised three issues with regard to claims 1 and 28.

First, the Examiner alleges that the phrase "or a SDF1 or I-TAC binding fragment" renders the claim indefinite because it is unclear whether or not SDF-1 or I-TAC need be present when the agent is contacted with the receptor, or whether the agent is contacted with either SDF-1 or I-TAC, or the CCX-CKR2 polypeptide. *See*, page 7, item 5a of the Office Action. Specifically, the Examiner contends that it is unclear how the agent would compete with SDF-1 or I-TAC for binding if contacted with the receptor alone. With regard to this issue, Applicants believe that the amendment to claim 1 is sufficient to address the Examiner's concerns.

The second issue raised by the Examiner concerns the "metes and bounds" of a fragment. Specifically, the Examiner contends that the "metes and bounds" of a fragment recited in claims 1 and 28 are unclear. *See*, page 7 of the Office Action. Applicants direct the Examiner's attention to page 23, lines 4 to 12, of the specification. Specifically, the passage

states that fragments can be any fragment capable of binding the CCX-CKR2 ligands (e.g., SDF-1 or I-TAC). The passage provides further guidance stating that "CCX-CKR2 fragments can include any fragment of e.g., at least 20, 30, 40, 50 amino acids up to a protein containing all but one amino acid of CCX-CKR2. Typically, ligand binding fragments will comprise transmembrane regions and/or most or all of the extracellular domains of CCX-CKR2." *See,* page 23, lines 8-12 of the specification. In light of the above, Applicants believe that the metes and bounds of a fragment are sufficiently disclosed.

The third issue raised by the Examiner is that claim 28 is incomplete for omitting essential steps amounting to a gap between the steps (MPEP §2172.01). Specifically, the Examiner alleges that the claim does not recite whether SDF-1 or I-TAC ligands are present when the cell expressing the CCX-CKR2 polypeptide comprising the extracellular domain of SEQ ID NO:2 is contacted with an agent. The Examiner also inquired as to the difference in scope between claim 1 and claim 28.

With regard to this issue, Applicants point out that Claim 1 is directed to a method comprising two steps. The first step is contacting the polypeptide with *a plurality of agents*, and a second step of *selecting an agent* that competes with SDF-1 or I-TAC for binding.

Claim 28, on the other hand, is directed to a method comprising contacting a cell that expresses a CCX-CKR2 polypeptide with an agent that binds the polypeptide and that "competes with SDF1 or I-TAC for binding to CCX-CKR2." The latter phrase refers to the ability of the agent to compete with SDF1 or I-TAC, if present, and thus does not require the presence of SDF1 or I-TAC. It is not clear why the Examiner believes that claim 28 lacks an essential step. What step is missing?

Claims 2-10 and 29-32 depend from independent claims 1 and 28 respectively, and therefore contain all of the limitations of the claims from which they depend. Therefore, the arguments recited above with regard to independent claims 1 and 28 are also applicable to dependent claims 2-10 and 29-32.

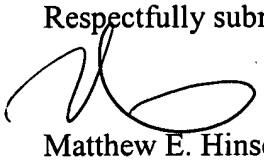
In light of the above, the Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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The dihydrofolate reductase gene (*dhfr*) is required to maintain cellular concentrations of H_4folate for nucleotide biosynthesis (see Chapter 13). Cells lacking this enzyme will only survive in media containing thymidine, glycine, and purines. Mutant cells (*dhfr*$^-$), which are transfected with the *dhfr* gene, therefore, can be selectively grown in a medium lacking these supplements. Expressing foreign genes in mutant cells, cotransfected with selectable markers, is limited to cell types that can be isolated with the required gene defect. Normal cells, however, transfected with a vector carrying the *dhfr* gene, are also resistant to methotrexate, an inhibitor of dihydrofolate reductase and these cells can be selected for by growth in methotrexate.

Another approach for selecting nonmutated cells involves the use of a bacterial gene coding for aminoglycoside 3′-phosphotransferase (APH) for cotransfection. Cells expressing APH are resistant to aminoglycoside antibiotics such as neomycin and kanamycin, which inhibits protein synthesis in both procaryotes and eucaryotes. Vectors carrying an *APH* gene, therefore, can be used as a selectable marker in both bacterial and mammalian cells.

Foreign Genes Can Be Expressed in Eucaryotic Cells by Utilizing Virus Transformed Cells

Figure 18.18 depicts the transient expression of a transfected gene in COS cells, one of the more commonly used systems to express foreign eucaryotic genes. The COS cells are permanently cultured simian cells, transformed with an origin-defective SV40 genome. The defective viral genome has integrated into the host cell genome and constantly expresses viral proteins. Infectious viruses which are normally lytic to infected cells are not produced because the viral origin of replication is defective. The SV40 proteins expressed by the transformed COS cell will recognize and interact with a normal SV40 ori carried in a vector transfected into these cells. These SV40 proteins will, therefore, promote the repeated replication of the vector. The transfected vector containing both an SV40 ori and a gene of interest may reach a copy number in excess of 10^5 molecules/cell. Transfected COS cells die after 3–4 days possibly due to a toxic overload of the episomal vector DNA.

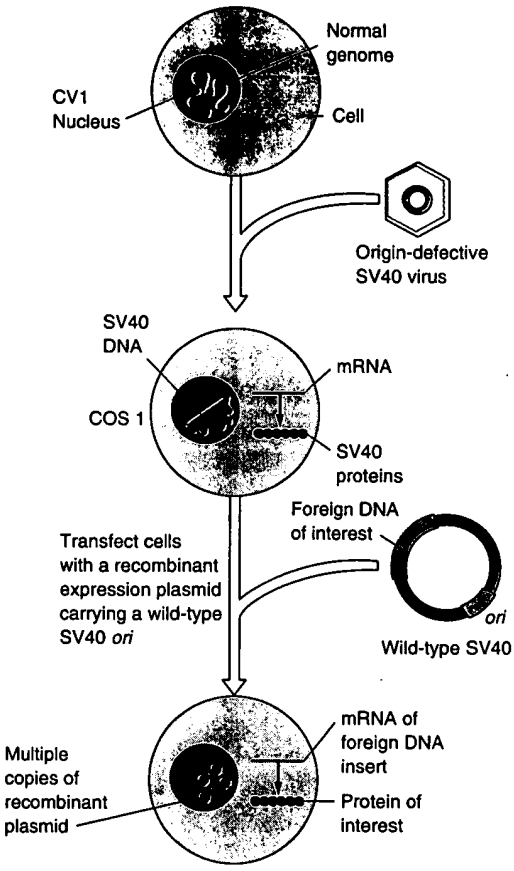

FIGURE 18.18
Expression of foreign genes in the eucaryotic COS cell.
CV1, an established tissue culture cell line of simian origin, can be infected and will support the lytic replication of the simian DNA virus, SV40. Cells are infected with an origin (*ori*)-defective mutant of SV40 whose DNA permanently integrate into the host CV-1 cell genome. The defective viral DNA continuously codes for proteins that can associate with a normal SV40 *ori* to regulate replication. Due to its defective ori, the integrated viral DNA will not produce viruses. The SV40 proteins synthesized in the permanently altered CV-1 cell line, COS-1, can, however, induce the replication of recombinant plasmids carrying a wild-type SV40 *ori* to a high copy number (as high as 10^5 molecules per cell). The foreign protein synthesized in the transfected cells may be detected immunologically or enzymatically.

18.12 SITE-DIRECTED MUTAGENESIS

By altering or mutating selected regions or single nucleotides within cloned DNA and using the technologies described above it is possible to define the role of DNA sequences in gene regulation and amino acid sequences in protein function. **Site-directed mutagenesis** is the controlled alteration of selected regions of a DNA molecule. It may involve the insertion or deletion of selected DNA sequences or the replacement of a specific nucleotide with a different base. A variety of chemical methods mutate DNA in vitro and in vivo, but these usually occur at random sites within the DNA molecule.

The Role of Flanking Regions in DNA Can Be Evaluated by Deletion and Insertion Mutations

Site-directed mutagenesis can be carried out in various regions of a DNA sequence including the gene itself or the flanking regions. Figure 18.19 depicts a simple deletion mutation strategy where the sequence of interest

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A → B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.